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Influence of gut microbiome on multiple myeloma: friend or foe?

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ABSTRACT

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells, which typically evolves over time from its precursor, monoclonal gammopathy of undetermined significance. While the underlying mechanisms of this evolution remain elusive, immunomodulatory factors affecting the bone marrow (BM) microenvironment are suspected to play a role. There is an increasing evidence that the gut microbiome exerts an influence on its host's adaptive and innate immune systems, inflammatory pathways and the BM microenvironment. Dysbiosis, therefore, may impact tumorigenesis in MM. This article gives an overview of potential mechanisms by which the microbiome may influence the pathogenesis of MM, MM patients' responses to treatment and toxicities experienced by MM patients undergoing autologous transplant. It also discusses the potential role of the mycobiome in MM, a less studied component of the microbiome.

We read with great interest the review by Muhammad Bilal Abid describing the evolving field of the human gut microbiome and its interplay with the immune system, tumorigenesis and chemoresistance.[1] Plasma cell malignancy, a cancer of the adaptive immune system, deserves special attention when it comes to the interface of gut microbiota and the immune system.

Historically, research on the gut microbiota has focused on bacteria; however, viruses, bacteriophages and fungi also contribute to its ecological diversity. The gut microbiome is under constant surveillance by our immune system and therefore changes in this ecosystem may lead to local and/or systemic inflammation. Local immune stimulation occurs in the lamina propria and mesenteric lymphatic system. Systemic immune activation occurs through several pathways, some of which are not completely understood. A growing body of evidence suggests that immune activity within the gut, influenced by the microbiome, has the capacity to impact immune cells in distant organs/the bone marrow (BM), and may play a role in myelomagenesis.

Multiple myeloma (MM) and its precursor monoclonal gammopathy of undetermined significance (MGUS) are characterized by accumulation of clonal, terminally differentiated plasma cells in the BM. While complex genetic abnormalities are associated with myelomagenesis, the BM microenvironment is also believed to play a role in disease progression.[2 3] The microenvironment consists of cellular components (stromal cells, osteoblasts, osteoclasts and immune cells) and non-cellular components (extracellular matrix proteins, growth factors and cytokines) which influence both stromal cells and plasma cells. Although progression from MGUS to active disease occurs through a complicated series of changes which appear to be non-linear, it is speculated that a 'permissive' microenvironment is likely to be associated with progression.[3 4] In fact, chronic antigen stimulation may be a mechanism which can affect BM microenvironment and promote progression of plasma cell dyscrasias. This is supported by observations that B7+ (CD80 +or CD86+) T cells are common in patients with MM. B7 expression, which is common on T cells with myeloma, is acquired by chronically stimulated T cells.[5] Another study suggested that CD4 +T cells in chronic autoimmunogenicity of the hyperphosphorylated paratarg-7 (pP-7) may be associated with development of MM.[6] It is also interesting to note that antigen-mediated stimulation has been postulated to increase clonal plasma cells in Gaucher disease-associated gammopathy and this clinical association should be investigated further to determine how chronic antigen stimulation influences myelomagenesis.[7]

The microbiome composition and metabolites also influence the BM microenvironment, and thereby, can affect myelomagenesis[8] Small studies have demonstrated that genus-level differences in microbiome composition exist in patients with MM compared with MGUS, suggesting that dysbiosis may

be associated with progression to MGUS and MM.[9] The influence of dysbiosis with BM microenvironment and hematopoiesis is demonstrated by a study by Kwon *et al* on Rag-1-deficient mice, where the Rag-1 deficient mice had downregulation of hematopoietic stem and progenitor cells (HSPCs) production resulting in a lymphopenic state. These mice were noted to have a different gut bacterial composition compared with wild type species. Metagenomic analysis demonstrated that fecal implantation led to microbiobial composition similar to wild type, and was associated with an increase in production of HSPCs to wild-type levels.[10]

An emerging mechanism by which microbiome can influence the BM microenvironment is through synthesis of bioactive metabolites such as short chain fatty acids (SCFAs). SCFAs can suppress nuclear factor kappa-light-chain enhancer of activated B cells (NF-ƙB) and proinflammatory cytokines like interleukin- 6 (IL-6), and tumor necrosis factor α (TNF-α); conversely they may increase IL-10, T helper 17 cells (Th17) and Th1 cells.[11] Moreover, Jian reported that SCFA producing bacteria were reduced and nitrogen recycling bacteria such as *Klebsiella spp* were significantly enriched in MM compared with healthy controls. The MM-enriched bacteria showed higher abundance in MM patients with International Staging System (ISS)-III than those of MM patients with ISS-II.[12]

Another mechanism by which gut microbiome may modulate the BM microenvironment is via cytokines. Plasma cells express IL-17 receptors and are stimulated in vitro and in vivo with IL-17.[2] IL-17 can influence BM microenvironment by upregulating receptor activator of nuclear factor kappa-B ligand on stromal cells and stimulating osteoclasts which can lead to development of bone lesions.[13] Calcinotto *et al* proposed a mechanism by which gut bacteria *Prevotella heparinolytica* was associated with progression of MM. *Prevotella heparinolytica* promoted the differentiation and migration of gut Th17 cells toward the BM of transgenic Vk*MYC mice, where they favored tumor progression and promoted development of MM. Lack of IL-17 in Vk*MYC mice delayed MM appearance. IL-17 levels in BM of VK*MYC mice was higher in MGUS and may be associated with progression of Smoldering MM to active MM.[14] Eosinophils are also activated by IL-17, resulting in production of various cytokines including IL-6 and TNF-α, which promote plasma cell proliferation and survival.[14] The above findings suggest the presence of an active gut-BM axis in pathogenesis of MM and warrants further investigation.

The gut microbiome also appears to influence treatment responses and therapy-related toxicities in MM patients. In 2019, Pianko *et al* demonstrated a higher relative abundance of *Eubacterium hallii* in MM patients with minimal residual disease (MRD) negativity after first induction as opposed to MRD-positive patients, suggesting that the composition of the microbiome after first induction may affect response to treatment.[15] Others have proposed mechanisms by which SCFA produced by gut microbiome may help minimize gastrointestinal toxicity due to proteasome inhibitors.[8] Similarly, in the transplant population, D'Angelo observed that patients with MM undergoing autologous stem cell transplant (ASCT) have decreased microbial diversity after transplant.[16] Furthermore, our group published results of a pilot study on gut microbiome and mycobiome composition in patients with MM undergoing autotransplant with melphalan conditioning. A higher stool *Bacteroides* population at day +7 was associated with less severe diarrhea, while higher prevalence of *Blautia* and *Ruminococcus* (members of the Firmicutes phylum and anaerobic *Clostridium* class) were associated with higher incidence of diarrhea and post-transplant nausea and vomiting. There was a negative association between presence of fungal phyla *Glomerella* and neutrophil engraftment. Although this study included only 15 patients, it supported prior observations that the bacterial microbiome affects therapy-related toxicities and introduced the possibility that the mycobiome plays a similar role.[17] Larger studies on roles of the microbiome and mycobiome in MM transplant toxicity and outcomes are would be beneficial in confirming these associations and study mechanisms.

The non-selective immunomodulator dexamethasone (DXM) is an essential component to most myeloma treatment regimens and its reciprocal interaction with human microbiota warrants investigation. Huang *et al* observed a change in the composition of the gut microbiota, specifically a higher prevalence of *Bifidobacterium* and *Lactobacillus* in mice with chronic steroid exposure as compared with controls; in contrast, *Mucispirillum*, a known colonic mucin degrader, was absent in the mice with chronic steroid exposure. Moreover, DXM-treated donor mice may have reduced IL-17 production compared with control donor mice.[18] Since IL-17 production is also mediated by gut flora, the changes in microbiota induced by chronic DXM use may contribute to the activity of this agent in treating DXM in myeloma.

To date, fungi have composed of a neglected part of the gut microbiome. The interaction between mycobiome and bacterial communities and the potential protective role of the former for whole human microbiota deserves special attention. While most studies focus on the gut bacteria, there is known interdependence and strategic evolutionary cooperation between bacteria and fungi. Biofilms are microbes including fungi and bacteria, embedded in a polymeric matrix that protects them from antimicrobials and resists host defenses. Biofilms shield the fungi from environmental factors and are associated with poor immune clearance by the host. Fungal filamentation is a known *Candida* virulence factor which damages host tissue and triggers host inflammatory response. Dysbiosis of gut bacteria can therefore interfere with mycobiome composition and the bacteria–fungi relationship may be another axis by which the gut bacteria influence systemic immunomodulation.[19] DXM may also affect the host mycobiome profile. The role of the mycobiome community and fungal pathogens in MM outcomes and

progression is not well understood. More studies are needed to understand the effects of DXM on gut fungi.

Studies on MM and microbiome are limited and while certain trends and observations have been made, like possible effect on microbiome on cytokines affecting BM microenvironment, role of SCFA on myelomagenesis and associations of microbiome on treatment toxicities, it may be premature to draw general conclusions based on available literature. A better understanding of dysbiosis, its role in disease propagation in MM, and its effects on response and toxicity, is essential. We summarize the current work on the microbiome and its perceived role in MM. AS we further understand the mechanisms on influence of the microbiome on the BM microenvironment, we hope that in the future, we could develop strategies to harness the microbiome to improve MGUS and MM outcomes.

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